S(-)RABEPRAZOLE COMPOSITIONS AND METHODS

Cross-Reference to Related Applications

[001] This application is a continuation of copending United States Patent Application Serial Number 10/ 263,558, filed October 2, 2002, which was a continuation of United States Patent Application Serial Number 10/082,571 (abandoned), filed February 25, 2002 as a continuation of United States Patent Application Serial Number 09/866,123 (abandoned), filed May 25, 2001 as a continuation of United States Patent Application Serial Number 09/675,418 (abandoned), filed April 28, 1999. United States Patent Application Serial Number 09/675,418 claimed the priority of United States Provisional Patent Application Serial Number 60/083,723 (expired), filed April 30, 1998. The entire contents of each of the prior applications is incorporated herein by reference.

Field of the Invention

[002] This invention relates to compositions of matter containing rabeprazole. The invention also relates to methods of treating and preventing ulcers, treating other conditions related to gastric hypersecretion, and treating psoriasis.

Background of the Invention

[003] Racemic rabeprazole is an orally active, potent, irreversible inhibitor of H^+, K^+-ATPase. The compound is one of the class of compounds known as gastric "proton pump" inhibitors. These compounds are weak organic bases which diffuse passively from the plasma into the acid-containing intracellular canaliculi of gastric parietal cells. At the low pH found in the lumen of these canaliculi, the protonated compounds rearrange to form pyridinium sulfenamides, which react with sulfhydryl groups present on the ATPase localized in the membranes lining the intracellular canaliculi. The alkylation of the sulfhydryl inhibits the ability of the enzyme to catalyze the secretion of H^+ into the lumen in exchange for K^+ ions. This inhibition results in an overall reduction in hydrochloric acid secretion by the parietal cells into the cavity of the stomach, thus increasing intra-gastric pH.

[004] As a consequence of reduced acidity in the stomach, the activity of the proteolytic enzyme pepsin is also markedly decreased. Because the proton pump is the final step in acid production and the compounds of this class combine covalently with the associated H^+,K^+-ATPase, a profound and prolonged inhibition of gastric acid secretion can be achieved.

[005] Proton pump inhibitors have also been reported as useful in treating psoriasis. *See*, for example, published International Application WO95/18612.

[006] The C_{max} of racemic rabeprazole is at about 4 to 5 hours in humans and the serum half-life is about 50 minutes to 1.5 hours depending on dose, but this does not reflect the duration of the acid inhibitory effect, which is about 24 hours. Racemic rabeprazole is comparable to omeprazole in its effects on hepatic drug metabolizing enzyme systems such as CYP 3A, although it appears to be less inhibitory of CYP 2C19 than is omeprazole and a more potent inducer of CYP 1A1 mRNA than is pantoprazole.

[007] No cardiovascular or obvious physical changes have been so far reported in humans on administration of racemic rabeprazole, but reports of clinical trials are only recently beginning to appear. Most proton pump inhibitors produce significantly elevated fasting serum gastrin levels. This is cause for concern because prolonged elevated serum gastrin appears to be associated with diffuse and focal enterochromaffin-like cell hyperplasia and focal neoplasia (carcinoids) in rats. Larsson *et al*, *Gastroenterology*, 90:391-399 (1986). Thus, despite its advantages, some adverse effects of racemic rabeprazole may remain, including, but not limited to, some incidence of hepatocellular neoplasia and gastric carcinoids on long-term therapy, and headache, diarrhea and skin alterations on acute therapy. It would therefore be particularly desirable to find a compound with the advantages of the racemic mixture of rabeprazole which would not have the aforementioned disadvantages.

Summary of the Invention

[008] This invention relates to the use of optically pure *S*(-)rabeprazole for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome, and other disorders including those that would benefit from an inhibitory action on gastric acid secretion. *S*(-)rabeprazole inhibits the H^+, K^+-ATPase associated with the gastric proton pump and the resulting secretion of gastric acid by parietal cells providing therapy in diseases associated with gastric hyperacidity. The invention also relates to a method of treating psoriasis using optically pure *S*(-)rabeprazole.

[009] Optically pure *S*(-)rabeprazole provides this treatment while substantially reducing adverse effects, including, but not limited to, hepatocellular neoplasia, gastrin hypersecretion, gastric neoplasms or carcinoids, headache, diarrhea and skin alterations which are associated with the administration of the racemic mixture of rabeprazole.

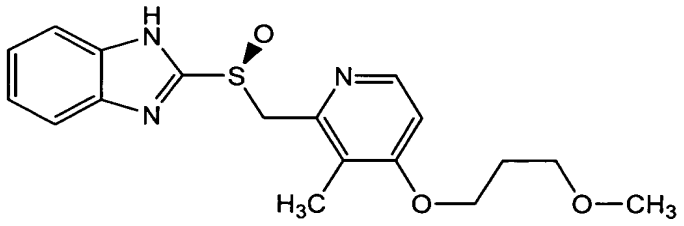
[010] The invention also relates to certain pharmaceutical compositions containing the *S*(-) isomer of rabeprazole.

Detailed Description of the Invention

[011] The active compound of these compositions and methods is an optical isomer of rabeprazole. The preparation of racemic rabeprazole is described in United States Patent 5,045,552 and its equivalent European Application 268956.

[012] Chemically, the active compound in the compositions and methods of the invention is the *S*(-) isomer of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl-[1H]-benzimidazole [hereinafter, "*S*(-)rabeprazole"]. *S*(-)rabeprazole is not presently commercially available.

[013] The structure of *S*(-)rabeprazole, which is not presently commercially available, is represented by formula **I**:



I

[014] The separation of racemic rabeprazole into *R*(+)rabeprazole and *S*(-) rabeprazole by chromatography has been described by Nochi *et al.*, *Chem. Pharm. Bull.*, 44:1853-1857 (1996), but the pharmacology and pharmacodynamics have not been described for either enantiomer.

[015] In addition to the chromatographic separation of the racemate into its enantiomers, asymmetric oxidation of the thioether precursor and bioreduction of the racemate to eliminate the *R*(+) enantiomer can be carried out in analogous fashion to the procedure described for lansoprazole in published International Applications WO 96/02535 and WO 96/17077; the disclosures of which are incorporated herein by reference.

[016] It has now been discovered that the optically pure *S*(-) isomer of rabeprazole is a superior agent for treating ulcers of the stomach, duodenum and esophagus, gastroesophageal reflux diseases, Zollinger-Ellison Syndrome, psoriasis and other disorders, including those that would benefit from an inhibitory action on H^+,K^+-ATPase in that it provides this effective treatment while substantially reducing the adverse effects of racemic rabeprazole including, but not limited to, hepatocellular neoplasia, gastric carcinoids, headache, diarrhea and skin alterations. The S(-) rabeprazole isomer is also a superior agent for treating ulcers and other disorders by virtue of the greater predictability of dosage among patients, as discussed below.

[017] The present invention encompasses a method of treating ulcers, wherein the method comprises administering to a human in need of such therapy, an amount of *S*(-)rabeprazole, or a pharmaceutically acceptable salt thereof, substantially free of its (+) stereoisomer, the amount being sufficient to alleviate the symptoms of ulcers. The method substantially reduces the concomitant liability of adverse effects associated with the administration of the racemic compound by providing an amount which is insufficient to cause the adverse effects associated with the racemic mixture of rabeprazole.

[018] The present invention also encompasses an oral anti-ulcer composition for the treatment of a human in need of anti-ulcer therapy, wherein the composition comprises a pharmaceutically acceptable carrier for oral administration and a therapeutically effective amount of *S*(-) rabeprazole, or a pharmaceutically acceptable salt thereof, substantially free of its *R*(+) stereoisomer. Preferably the composition is in the form of a tablet or capsule and the amount of *S*(-)rabeprazole in the tablet or capsule is 10, 30 or 50 mg.

[019] The present invention further encompasses a method of treating gastroesophageal reflux disease and other conditions caused by or contributed to by gastric hypersecretion. Conditions associated with hypersecretion in humans may include, but are not limited to, Zollinger-Ellison syndrome.

[020] The present invention further encompasses a method of treating psoriasis, while substantially reducing the adverse effects of racemic rabeprazole.

[021] Utilizing the optically pure or substantially optically pure *S*(-) isomer of rabeprazole results in enhanced efficacy, diminished adverse effects, and accordingly, an improved therapeutic index. Moreover, the *S*(-) enantiomer provides a desirable half-life and shows less variation in the patient population between so-called extensive metabolizers and poor metabolizers than does racemic rabeprazole. It is therefore, more desirable to use the *S*(-) isomer of rabeprazole than to administer the racemic mixture because predictability of an effective and safe dose for an individual patient is greater.

[022] The term "adverse effects" includes, but is not limited to, hepatocellular neoplasia, gastric hypersecretion, gastric carcinoids, headache, diarrhea and skin alterations.

[023] The term "substantially free of its *R*(+) stereoisomer", as used herein means that a particular rabeprazole composition contains at least 90% by weight of *S*(-)rabeprazole and 10% by weight or less of *R*(+) rabeprazole. In a more preferred embodiment the term "substantially free of its *R*(+) isomer" means that a rabeprazole composition contains at least 99% by weight of *S*(-)rabeprazole, and 1% or less of *R*(+)rabeprazole. These percentages are based upon the total amount of rabeprazole in the composition. The terms "substantially optically pure *S*(-) isomer of rabeprazole", "substantially optically pure *S*(-)rabeprazole", "optically pure *S*(-) isomer of rabeprazole"and "optically pure *S*(-)rabeprazole" are also encompassed by the above-described amounts.

[024] The term "treating ulcers", as used herein means treating, alleviating or palliating such conditions, and thus providing relief from the symptoms of nausea, heartburn, post-prandial pain, vomiting, and diarrhea.

[025] The term "a method for treating gastroesophageal reflux diseases in a human", as used herein means treating, alleviating or palliating the conditions that result from the backward flow of the stomach contents into the esophagus.

[026] The term "treating a condition caused, or contributed to, by gastric hypersecretion in a human", as used herein means treating, alleviating or palliating such disorders associated with gastric hypersecretion, thus providing relief from the symptoms of the aforementioned conditions. Zollinger-Ellison Syndrome is among the conditions caused by or contributed to by gastric hypersecretion.

[027] The term "treating psoriasis", as used herein means treating, alleviating or palliating the condition, thereby providing relief from the symptoms associated with the condition, such as, for example, pruritus, epidermal scaling, itching and burning.

[028] The magnitude of a prophylactic or therapeutic dose of *S*(-)rabeprazole in the acute or chronic management of disease will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for *S*(-)rabeprazole for the conditions described herein is from about 5 mg to about 200 mg in single or divided doses. Preferably a daily dose range should be about 10 mg to about 50 mg in single or divided doses.

[029] In managing the patient, the therapy should be initiated at a lower dose, perhaps at about 10 mg to about 15 mg and increased up to about 50 mg or higher depending on the patient's global response. It is further recommended that children and patients over 65 years and those with impaired renal or hepatic function, initially receive low doses, and that they be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response.

[030] The terms "an amount sufficient to alleviate or palliate ulcers but insufficient to cause said adverse effects," "an amount sufficient to alleviate the symptoms of gastroesophageal reflux but insufficient to cause said adverse effects," "an amount sufficient to alleviate gastric hypersecretion but insufficient to cause said adverse effects" and "an amount sufficient to treat psoriasis" are encompassed by the above-described dosage amounts and dose frequency schedule.

[031] The relative activity, potency and specificity of optically pure rabeprazole and racemic rabeprazole both as gastric anti-secretory agents and plasma gastrin elevating agents can be determined by a pharmacological study in animals according to the method of Decktor *et al.*, *Journal Pharmacol. Exp. Ther.*, 1-5 (1989). The test provides an estimate of relative activity, potency and, through a measure of specificity, an estimate of therapeutic index. Fasted rats, implanted with a gastric cannula, receive single oral or

parenteral doses of *R*(+)rabeprazole,
S(-)rabeprazole or the racemate, 1 hour before collection of gastric juice over a four hour period. Acid output and pH are then determined on each sample.

[032] Dose response evaluations are performed with each compound to determine the lowest dose which inhibits acid output by at least 95% and maintains gastric pH above 7.0. Plasma gastrin levels are then determined in a second group of rats treated with the doses selected in the first series of tests. Blood samples are taken for analyses over the five hour period after dosing, and both peak level as well as area-under-the-curve analyses of the gastrin responses are made. These responses are then analyzed statistically using Student's "t" test to assess whether equivalent anti-secretory doses show differences in gastrin responses.

[033] Any suitable route of administration may be employed for providing the patient with an effective dosage of *S*(-)rabeprazole. Rectal, transdermal, parenteral (subcutaneous, intravenous, intramuscular), and like, are possible routes of administration, but oral administration is preferred. Oral dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, and the like.

[034] The pharmaceutical compositions of the present invention comprise *S*(-)rabeprazole as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic ingredients.

[035] The terms "pharmaceutically acceptable salts" and "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic bases. Since the compound of the present invention is a weak acid and is unstable at low pH, salts may be prepared from pharmaceutically acceptable non-toxic bases including inorganic and organic bases. Suitable pharmaceutically acceptable base addition salts for the compound

of the present invention include metallic salts of aluminum, calcium, lithium, magnesium, potassium, sodium, titanium and zinc or organic salts made from lysine, *N,N'*-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (*N*-methylglucamine) and procaine. Sodium salts are especially preferred.

[036] The compositions of the present invention include suspensions, solutions, elixirs or solid dosage forms. Carriers such as starches, sugars, and microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like are suitable in the case of oral solid preparations (such as powders, capsules, and tablets), and oral solid preparations are preferred over the oral liquid preparations. It has been found that the inclusion of mannitol and of basic salts of calcium and magnesium in the compositions allows the preparation of tablets and capsules that retain good stability.

[037] If desired, tablet and granule formulations may be coated by standard aqueous or non-aqueous techniques. Oral dosage forms suitable for rabeprazole are described, for example, in United States Patent 5,035,899 and in published International Applications WO 96/01624, WO 97/12580 and WO 97/25030, the disclosures of which are incorporated herein by reference.

[038] In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release formulations, which are well known in the art. Compositions suitable for rectal administration are described, for example, in European Application 645140, the disclosure of which is incorporated herein by reference.

[039] Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active

ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

[040] For example, a tablet may be prepared by compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

[041] Desirably, each tablet dosage will contain from about 10 mg to about 100 mg of the active ingredient, and each cachet or capsule contains from about 10 mg to about 100 mg of the active ingredient. Most preferably, the tablet, cachet or capsule contains either one of three dosages, about 10 mg, about 30 mg or about 50 mg of *S*(-)rabeprazole for oral administration.

[042] The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

Example 1

Tablets - Composition per Tablet	
S(-)rabeprazole	30.0 mg
Precipitated calcium carbonate	50.0 mg
Corn Starch	40.0 mg
Lactose	73.4 mg
Hydroxypropylcellulose	6.0 mg
Magnesium stearate	(0.05 ml)
Total	200.0 mg

[043] *S*(-)rabeprazole, precipitated calcium carbonate, corn starch, hydroxypropylcellulose and lactose are mixed together, water is added, and the mixture is kneaded, then dried in vacuum at 40E C for 16 hrs; ground in a mortar and passed through a 16-mesh sieve to give granules. To this is added magnesium stearate and the resultant mixture is made up into tablets each weighing 200.0 mg on a rotary tableting machine. Enteric-coated tablets may be prepared by spray-coating the above tablets with an enteric coating, such as, for example, a polyacrylate Eudragit L® or Eudragit S® polymer, preferably in the form of an aqueous dispersion.

Example 2

Granules - Composition per Tablet:	
S(-)rabeprazole	30.0 mg
Magnesium carbonate	20.0 mg
Corn Starch	80.0 mg
Microcrystalline cellulose	20.0 mg
Carboxymethylcellulose calcium	10.0 mg
Hydroxypropylcellulose	10.0 mg
Pluronic F68	4.0 mg
Lactose	26.0 mg
Water	(0.05 ml)
Total	200.0 mg

[044] The ingredients above are mixed well in the proportions shown; water is added, and the mixture is kneaded and granulated in an extruder granulator (screen size 1.0 mm N). The granules are immediately converted to spherical form in a spheronizer. The spherical granules are then dried under vacuum at 40E C for 16 hrs and passed through round sieves to give 12- to 42-mesh granules.

Example 3

Capsules of Enteric-Coated Granules - Composition per Capsule	
Enteric Coating for Granules	
Eudragit L-30D	138.0 mg (41.4 mg solids)
Talc	4.1 mg
PEG 5000	12.4 mg
Tween 80	2.1 mg
Water	276 Φl
Enteric-Coated Granules	
Granules according to Example 2	200.0 mg
Enteric Coating	60.0 mg
	260.0 mg
Capsules of Enteric-Coated Granules	
Enteric-coated granules	260.0 mg
No. 1 hard capsule	76.0 mg
	336.0 mg

[045] Enteric-coated granules are produced by coating the granules obtained in Example 2 with the enteric coating composition shown using a fluidized bed granulator under conditions such that the inlet air temperature is 50E C and the granule temperature is about 40E C. Number 1 hard capsules are filled with the enteric-coated granules in an amount of 260.0 mg per capsule using a capsule filling machine.

[046] Tablets and/or capsules of other strengths may be prepared by altering the ratio of active ingredient to the excipients or to the final weight of the dosage form.